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EP 0773023 A **WO 2004/074286 A1**
WO 2003/044015 A

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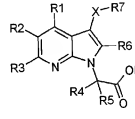
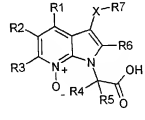
Other: **CAS ONLINE, WPI, EPODOC, TXTE**

(54) Abstract Title: **Pyrrolopyridines and their use in the treatment of diseases mediated by PGD2 at the CRTH2 receptor**

(57) Compounds of formula (Ia) or (Ib):



Ia



Ib

wherein

R^1, R^2 and R^3 are independently hydrogen, halo, -C_1-C_6 alkyl, -O(C_1-C_6 alkyl), -C_1-C_6 alkyl(C_3-C_7 cycloalkyl), -CON(R^8)$_2$, -SOR^8, -SO^2R^8, -$SO_2N(R^8)_2$, -$N(R^8)_2$, -NR^9COR^8, -CO_2R^8 , COR^8, -SR^8, -OH, -NO_2 or -CN;

each R^8 is independently hydrogen or C_1-C_6 alkyl;

R^4 and R^5 are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group;

R_6 is hydrogen or C_1-C_6 alkyl;

R^7 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or an aromatic moiety, any of which may optionally be substituted with one or more substituents selected from halo, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, -R^{10}, -OR^{10}, C(R^{10})$_2$ -CON(R^{10})$_2$, -SOR^{10} -SO_2R^{10}, - $SO_2N(R^{10})_2$, -$N(R^{10})_2$, -$NR^{10}COR^{10}$, -CO_2R^{10}, -COR^{10}, -SR^{10}, -OH, -NO_2 or -CN;

wherein each R^{10} is independently hydrogen, C_1-C_6 alkyl, aryl or substituted aryl;

X is -S- or -SO_2-; or pharmaceutically acceptable salts, hydrates, solvates, complexes or prodrugs thereof are useful in the treatment of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis.

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COMPOUNDS

The present invention relates to compounds which are useful as pharmaceuticals, to methods for preparing these compounds, compositions containing them and their use in the treatment and prevention of allergic diseases such as asthma, allergic rhinitis and atopic dermatitis and other inflammatory diseases mediated by prostaglandin D_2 (PGD_2) acting at the CRTH2 receptor on cells including eosinophils, basophils and Th2 lymphocytes

PGD_2 is an eicosanoid, a class of chemical mediator synthesised by cells in response to local tissue damage, normal stimuli or hormonal stimuli or *via* cellular activation pathways. Eicosanoids bind to specific cell surface receptors on a wide variety of tissues throughout the body and mediate various effects in these tissues PGD_2 is known to be produced by mast cells, macrophages and Th2 lymphocytes and has been detected in high concentrations in the airways of asthmatic patients challenged with antigen (Murray *et al*, (1986), *N. Engl. J. Med.* **315** 800-804) Instillation of PGD_2 into airways can provoke many features of the asthmatic response including bronchoconstriction (Hardy *et al*, (1984) *N. Engl. J. Med.* **311** 209-213, Sampson *et al*, (1997) *Thorax* **52** 513-518) and eosinophil accumulation (Emery *et al*, (1989) *J. Appl. Physiol.* **67** 959-962).

The potential of exogenously applied PGD_2 to induce inflammatory responses has been confirmed by the use of transgenic mice overexpressing human PGD_2 synthase which exhibit exaggerated eosinophilic lung inflammation and Th2 cytokine production in response to antigen (Fujitani *et al*, (2002) *J. Immunol.* **168** 443-449)

The first receptor specific for PGD_2 to be discovered was the DP receptor which is linked to elevation of the intracellular levels of cAMP However, PGD_2 is thought to mediate much of its proinflammatory activity through interaction with a G protein-coupled receptor termed CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) which is expressed by Th2 lymphocytes, eosinophils and basophils (Hirai *et al*, (2001) *J. Exp. Med.* **193** 255-261, and EP0851030 and EP-A-

1211513 and Bauer *et al*, EP-A-1170594) It seems clear that the effect of PGD_2 on the activation of Th2 lymphocytes and eosinophils is mediated through CRTH2 since the selective CRTH2 agonists 13,14 dihydro-15-keto-PGD_2 (DK-PGD_2) and 15R-methyl-PGD_2 can elicit this response and the effects of PGD_2 are blocked by an anti-CRTH2 antibody (Hirai *et al*, 2001, Monneret *et al*, (2003) *J. Pharmacol. Exp. Ther.* **304** 349-355) In contrast, the selective DP agonist BW245C does not promote migration of Th2 lymphocytes or eosinophils (Hirai *et al*, 2001; Gervais *et al*, (2001) *J. Allergy Clin. Immunol.* **108** 982-988). Based on this evidence, antagonising PGD_2 at the CRTH2 receptor is an attractive approach to treat the inflammatory component of Th2–dependent allergic diseases such as asthma, allergic rhinitis and atopic dermatitis

EP-A-1170594 suggests that the method to which it relates can be used to identify compounds which are of use in the treatment of allergic asthma, atopic dermatitis, allergic rhinitis, autoimmune disease, reperfusion injury and a number of inflammatory conditions, all of which are mediated by the action of PGD_2 at the CRTH2 receptor

Compounds which bind to CRTH2 are taught in WO-A-03/066046 and WO-A-03/066047 These compounds are not new but were first disclosed, along with similar compounds, in GB 1356834, GB 1407658 and GB 1460348, where they were said to have anti-inflammatory, analgesic and antipyretic activity WO-A-03066046 and WO-A-03066047 teach that the compounds to which they relate are modulators of CRTH2 receptor activity and are therefore of use in the treatment or prevention of obstructive airway diseases such as asthma, chronic obstructive pulmonary disease (COPD) and a number of other diseases including various conditions of bones and joints, skin and eyes, GI tract, central and peripheral nervous system and other tissues as well as allograft rejection

WO-A-03/101961 and WO-A-2004/007451 also relate to compounds which are CRTH2 receptor antagonists The compounds disclosed in both these documents are indole-1-carboxylic acid derivatives with the compounds described in WO-A-

03/101961 having an S-aryl group and the compounds of WO-A-2004/007451 having either SO-aryl or SO_2-aryl at the 3-position of the indole ring system

Other compounds which are CRTH2 receptor antagonists are disclosed in our co-pending applications PCT/GB2004/004336, which relates to indole-1-acetic acid derivatives, PCT/GB2004/04337, which relates to indole-1-sulfonyl-3-acetic acid derivatives, and PCT/GB2004/004417, which relates to indole-1-acetic acid derivatives.

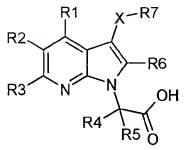
Indole-1-carboxylic acid derivatives are also disclosed in WO-A-99/50268 In this case, the compounds have a –alkylaryl group at the 3-position of the indole system There is no suggestion that these compounds could be useful in the treatment of conditions such as asthma and allergic conditions, which are mediated by PGD_2 Rather, they are said to be of use in the treatment of complications arising from diabetes mellitus

WO-A-96/03376 relates to indole-1-carboxamides and hydrazides with a variety of substituents at the 3-position, including –alkylaryl groups These compounds are said to be $sPLA_2$ inhibitors

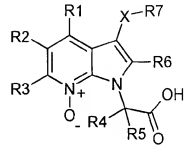
PL 65781 and JP 43-24418 also relate to indole derivatives which are similar in structure to indomethacin and, like indomethacin, are said to have anti-inflammatory and antipyretic activity Thus, although this may not have been appreciated at the time when these documents were published, the compounds they describe are COX inhibitors, an activity which is quite different from that of the compounds of the present invention Indeed, COX inhibitors are contraindicated in the treatment of many of the diseases and conditions, for example inflammatory bowel disease for which the compounds of the present invention are useful, although they may sometimes be used to treat arthritic conditions

The present invention relates to a novel group of compounds which have been found to have activity as CRTH2 receptor antagonists

In a first aspect of the present invention there is provided a compound of general formula (Ia) or (Ib)



Ia



Ib

wherein

R^1, R^2 and R^3 are independently hydrogen, halo, -C_1-C_6 alkyl, -O(C_1-C_6 alkyl), -C_1-C_6 alkyl(C_3-C_7 cycloalkyl), -CON(R^8)$_2$, -SOR^8, -SO_2R^8, -SO_2N(R^8)$_2$, -N(R^8)$_2$, -NR^8COR^8, -CO_2R^8, COR^8, -SR^8, -OH, -NO_2 or -CN;

each R^8 is independently hydrogen or C_1-C_6 alkyl,

R^4 and R^5 are each independently hydrogen, or C_1-C_6 alkyl or together with the carbon atom to which they are attached form a C_3-C_7 cycloalkyl group,

R^6 is hydrogen or C_1-C_6 alkyl,

R^7 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or an aromatic moiety, any of which may optionally be substituted with one or more substituents selected from halo, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, -R^{10}, -OR^{10}, C(R^{10})$_2$ -CON(R^{10})$_2$, -SOR^{10} -SO_2R^{10}, -SO_2N(R^{10})$_2$, -N(R^{10})$_2$, -NR^{10}COR^{10}, -CO_2R^{10}, -COR^{10}, -SR^{10}, -OH, -NO_2 or -CN,

wherein each R^{10} is independently hydrogen, C_1-C_6 alkyl, aryl or substituted aryl,

X is -S- or -SO_2-;

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof

The compounds of general formula (Ia) and (Ib) are antagonists of PGD_2 at the CRTH2 receptor and will therefore be useful in the treatment of conditions which are mediated by PGD_2 binding to CRTH2 These include allergic diseases, asthmatic conditions and inflammatory diseases, examples of which are allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitis, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease, as well as rheumatoid arthritis, psoriatic arthritis and osteoarthritis

In the present specification "C_1-C_6 alkyl" refers to a straight or branched saturated hydrocarbon chain having one to six carbon atoms and optionally substituted with one or more halo substituents or with one or more C_3-C_7 cycloalkyl groups Examples include methyl, ethyl, n-propyl, isopropyl, t-butyl, n-hexyl, trifluoromethyl, 2-chloroethyl, methylenecyclopropyl, methylenecyclobutyl, methylenecyclobutyl and methylenecyclopentyl.

"C_1-C_4 alkyl" and "C_1-C_{18} alkyl" have similar meanings except that they contain from one to four and from one to eighteen carbon atoms respectively

"C_2-C_6 alkenyl" and "C_1-C_6 alkynyl" refer to straight or branched carbon chains having from one to six carbon atoms and containing respectively a carbon-carbon double bond and a carbon-carbon triple bond The groups are optionally substituted with one or more halo substituents or with one or more C_3-C_7 cycloalkyl groups Examples include ethenyl, ethynyl, 2-propenyl and 2-propynyl

C_3-C_7 cycloalkyl refers to a saturated 3 to 7 membered carbocyclic ring. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl

In the present specification, "halo" refers to fluoro, chloro, bromo or iodo

The terms "aromatic moiety" and "aryl" and the abbreviation "Ar" in the context of the present specification refer to an aromatic ring system having from 5 to 14 ring carbon atoms and containing up to three rings, one or more of which may be replaced by a nitrogen, oxygen or sulphur atom Examples of aromatic moieties are benzene, pyridine, naphthalene, biphenyl, quinoline, isoquinoline, quinazoline, benzthiazole, benzoxazole, benzimidazole indole, indazole and imidazole ring systems

References to "substituted aryl" refer to an aryl moiety substituted with halo, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, $-CON(R^{10})_2$, $-SOR^{10}$ $-SO_2R^{10}$, $-SO_2N(R^{10})_2$, $-N(R^{10})_2$, $-NR^{10}COR^{10}$, $-CO_2R^{10}$, $-COR^{10}$, $-SR^{10}$, -OH, $-NO_2$ or -CN, where R^{10} is as defined above, provided that it is not substituted aryl

In all cases where a substituent contains two or more R^{10} groups, particularly when they are attached to the same nitrogen atom, it is preferred that at least one of the R^{10} groups is hydrogen or C_1-C_6 alkyl More preferably, at least one of the groups is hydrogen or C_1-C_4 alkyl and it is particularly preferred that at least one of the R^{10} groups is hydrogen.

Appropriate pharmaceutically and veterinarily acceptable salts of the compounds of general formulae (Ia) and (Ib) include basic addition salts such as sodium, potassium, calcium, aluminium, zinc, magnesium and other metal salts as well as choline, diethanolamine, ethanolamine, ethyl diamine and other well known basic addition salts

Where appropriate, pharmaceutically or veterinarily acceptable salts may also include salts of organic acids, especially carboxylic acids, including but not limited to acetate, trifluoroacetate, lactate, gluconate, citrate, tartrate, maleate, malate,

pantothenate, adipate, alginate, aspartate, benzoate, butyrate, digluconate, cyclopentanate, glucoheptanate, glycerophosphate, oxalate, heptanoate, hexanoate, fumarate, nicotinate, palmoate, pectinate, 3-phenylpropionate, picrate, pivalate, proprionate, tartrate, lactobionate, pivolate, camphorate, undecanoate and succinate, organic sulphonic acids such as methanesulphonate, ethanesulphonate, 2-hydroxyethane sulphonate, camphorsulphonate, 2-naphthalenesulphonate, benzenesulphonate, p-chlorobenzenesulphonate and p-toluenesulphonate, and inorganic acids such as hydrochloride, hydrobromide, hydroiodide, sulphate, bisulphate, hemisulphate, thiocyanate, persulphate, phosphoric and sulphonic acids

Salts which are not pharmaceutically or veterinarily acceptable may still be valuable as intermediates

Prodrugs are any covalently bonded compounds which release the active parent drug according to general formula (Ia) and (Ib) *in vivo* Examples of prodrugs include alkyl esters of the compounds of general formula (Ia) and (Ib), for example the esters of general formula (IIa) and (IIb) below.

If a chiral centre or another form of isomeric centre is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereoisomers, are intended to be covered herein Compounds of the invention containing a chiral centre may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone.

In the compounds of general formula (Ia) and (Ib), it is preferred that, independently or in any combination

R^1 is halo or hydrogen,

R^2 is halo or hydrogen,

R^3 is halo or hydrogen,

In preferred compounds of general formula (Ia) and (Ib), R^4 and R^5 are each independently hydrogen or C_1-C_4 alkyl However, in more active compounds, at least one, and preferably both of R^4 and R^5 are hydrogen

Compounds of general formula (Ia) and (Ib) preferably have an R^6 group chosen from H or C_1-C_6 alkyl, most suitably R^6 is hydrogen, methyl or ethyl

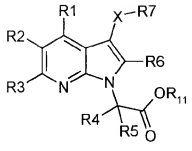
In more active compounds of the present invention R^7 is an aromatic moiety having one or two rings and substituted with one or more substituents selected from halo, $-C_1$-C_4 alkyl, $-O(C_1$-C_4 alkyl), $-SO_2(C_1$-C_4 alkyl), $-R^{10}$ and $-OR^{10}$, where R^{10} is preferably aryl or substituted aryl

Among the most preferred compounds are the following

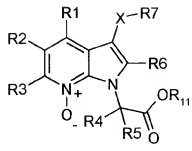
1 [3-(4-Chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
2 [5-Chloro-3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid;
3 [3-(4-Chloro-phenylsulfanyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
4 [3-(4-Chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid
5 [5-Chloro-3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
6 [3-(4-Chloro-benzenesulfonyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,

or a C_1-C_4 alkyl ester of one of the above

In a further aspect of the present invention, there is provided a compound of general formula (IIa) or (IIb).



IIa



IIb

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined for general formula (Ia) and (Ib), and R^{11} is C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{12})_2$, $CH((CH_2)_mO(C=O)R^{13})_2$,

m is 1 or 2,

R^{12} is hydrogen or methyl,

R^{13} is C_1-C_{18} alkyl

Compounds of general formulae (IIa) and (IIb) are novel and may be used as prodrugs for compounds of general formula (Ia) and (Ib) When the compound of general formula (IIa) or (IIb) acts as a prodrug, it is later transformed to the drug by the action of an esterase in the blood or in a tissue of the patient

Examples of particularly suitable R^{11} groups when the compound of general formula (IIa) or (IIb) is used as a prodrug include

methyl, ethyl, propyl, phenyl, $CH_2OC(=O)tBu$, $CH_2CH_2N(Me)_2$ $CH_2CH_2NH_2$ or $CH(CH_2O(C=O)R^{13})_2$ wherein R^{13} is as defined above.

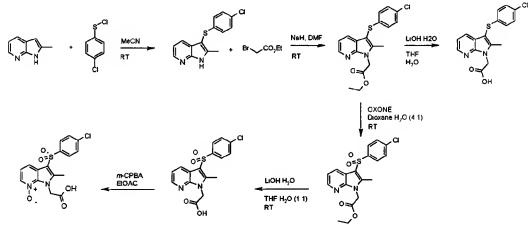
Other preferred substituents are as detailed for general formulae (Ia) and (Ib) above

In addition to their use as prodrugs, compounds of formula (IIa) and (IIb) wherein R^{11} is C_1-C_6 alkyl may be used in a process for the preparation of a compound of general formula (Ia) or (Ib), the process comprising reacting the compound of general formula (IIa) or (IIb) with a base such as sodium hydroxide or lithium hydroxide The reaction may take place in an aqueous solvent or an organic solvent

or a mixture of the two. A typical solvent used for the reaction is a mixture of tetrahydrofuran and water

Compounds of general formula (Ib) may also be prepared from compounds of general formula (Ia) by oxidation The oxidation may be achived using an oxidising agent such as a peroxyacid, for example 3-chloroperoxybenzoic acid (m-CPBA) Typically, the reaction will be conducted at room temperature in an organic solvent such as ethyl acetate A similar method can also be used for the conversion of compounds of general formula (IIa) to compounds of general formula (IIb)

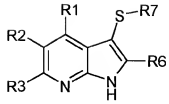
A synthetic route to example compounds of general formulae (Ia) and (Ib) is set out in Scheme 1



Scheme 1

Compounds of general formula (IIa) in which X is SO_2 may be prepared from the corresponding compounds of general formula (IIa) in which X is S by reaction with an oxidising agent such as potassium peroxymonosulphate, which is sold under the trade mark Oxone

Compounds of general formula (IIa) in which X is S may be prepared from compounds of general formula (III)



III

wherein R^1, R^2, R^3, R^6 and R^7 are as defined for general formula (Ia) and (Ib) by reaction with a compound of general formula (IV)

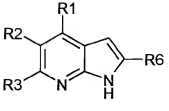
$$Z\text{-}C(R^4R^5)\text{-}CO_2R^{11} \qquad (IV)$$

wherein R^4 and R^5 are as defined for general formula (Ia) and (Ib) and Z is a leaving group in particular a halo group, for example chloro or bromo

The reaction is conducted under strongly basic conditions, for example using a metal hydride such as sodium hydride Suitable solvents include organic solvents such as dimethylformamide (DMF)

Compounds of general formula (IV) are well known and are readily available or can be prepared by methods known to those skilled in the art

Compounds of general formula (III) may be prepared by reacting a compound of general formula (V).



V

wherein R^6 is as defined for general formulae (Ia) and (Ib),

with a compound of general formula (VI)

$$Y\text{-}S\text{-}R^7 \qquad (VI)$$

where R^7 is as defined for general formulae (Ia) and (Ib) and Y is chloro, bromo or iodo

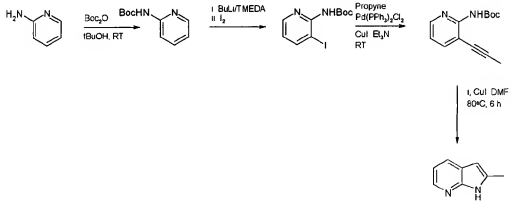
The reaction may be conducted at room temperature in a polar organic solvent such as acetonitrile

Compounds of general formula (VI) may be prepared from thiols of general formula (VII)

$$HS\text{-}R^7 \qquad (VII)$$

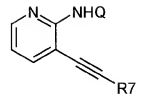
where R^7 is as defined for general formulae (Ia) and (Ib) by reaction with a halogenating agent such as N-bromosuccinimide or N-chlorosuccinimide. The reaction takes place at room temperature and may be conducted in a suitable organic solvent such as toluene

A synthetic route to an example of a pyrrolo[2,3-b]pyridine compound of general formula (V) is illustrated in Scheme 2 below



Scheme 2

As illustrated in Scheme 2, compounds of general formula (V) may be prepared from a protected 3-alkynyl-pyridin-2-yl amine of general formula (VIII)



VIII

wherein R^7 is as defined for general formulae (Ia) and (Ib) and Q is a suitable protecting group such as tert-butoxycarbonyl (Boc) by heating in the presence of a copper (I) salt, for example copper (I) iodide. Suitably, the reaction is carried out in an organic solvent such as dimethyl formamide (DMF).

Compounds of general formula (VIII) may be prepared by reacting 3-iodo-2-aminopyridine in which the amino group is protected by a suitable group such as t-butoxycarbonyl (Boc), with a compound of general formula (IX)

$$CH{\equiv}C\text{-}R^7 \qquad (IX)$$

wherein R^7 is as defined for general formulae (Ia) and (Ib)

The reaction is suitably carried out in the presence of a copper (I) salt, in particular copper (I) iodide.

Compounds of general formula (IX) are well known in the art and are readily available or can be prepared by known methods.

Amine-protected 3-iodo-2-aminopyridine is also well known in the art and can be prepared by known methods, for example by protecting 2-aminopyridine with a protecting group such as Boc, then deprotonating the protected compound with *n*-butyllithium then reacting with iodine

Compounds of general formula (Ia) and (Ib) are antagonists of PGD_2 at the CRTH2 receptor and compounds of general formula (IIa) and (IIb) are prodrugs for compounds of general formula (Ia) and (Ib) Compounds of general formulae (Ia) and (Ib) and (IIa) and (IIb)are therefore useful in a method for the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor, the method comprising administering to a patient in need of such treatment a suitable amount of a compound of general formula (Ia), (Ib), (IIa) or (IIb).

In a third aspect of the invention, there is provided a compound of general formula (Ia), (Ib), (IIa) or (IIb) for use in medicine, particularly for use in the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

Furthermore, there is also provided the use of a compound of general formula (Ia), (Ib), (IIa) or (IIb) in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor

As mentioned above, such diseases and conditions include allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis), conjunctivitis, especially allergic conjunctivitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis and also other PGD_2-mediated diseases, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease, as well as rheumatoid arthritis, psoriatic arthritis and osteoarthritis

The compounds of general formula (Ia), (Ib), (IIa) or (IIb) must be formulated in an appropriate manner depending upon the diseases or conditions they are required to treat

Therefore, in a further aspect of the invention there is provided a pharmaceutical composition comprising a compound of general formula (Ia), (Ib), (IIa) or (IIb)

together with a pharmaceutical excipient or carrier Other active materials may also be present, as may be considered appropriate or advisable for the disease or condition being treated or prevented

The carrier, or, if more than one be present, each of the carriers, must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient

The formulations include those suitable for oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration and may be prepared by any methods well known in the art of pharmacy

The route of administration will depend upon the condition to be treated but preferred compositions are formulated for oral, nasal, bronchial or topical administration.

The composition may be prepared by bringing into association the above defined active agent with the carrier In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product The invention extends to methods for preparing a pharmaceutical composition comprising bringing a compound of general formula (Ia), (Ib), (IIa) or (IIb) in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle

Formulations for oral administration in the present invention may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of the active agent, as a powder or granules, as a solution or a suspension of the active agent in an aqueous liquid or a non-aqueous liquid, or as an oil-in-water liquid emulsion or a water in oil liquid emulsion, or as a bolus etc

For compositions for oral administration (e g tablets and capsules), the term "acceptable carrier" includes vehicles such as common excipients e g binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, polyvinylpyrrolidone (Povidone), methylcellulose, ethylcellulose, sodium carboxymethylcellulose, hydroxypropylmethylcellulose, sucrose and starch, fillers and carriers, for example corn starch, gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride and alginic acid, and lubricants such as magnesium stearate, sodium stearate and other metallic stearates, glycerol stearate stearic acid, silicone fluid, talc waxes, oils and colloidal silica Flavouring agents such as peppermint, oil of wintergreen, cherry flavouring and the like can also be used. It may be desirable to add a colouring agent to make the dosage form readily identifiable. Tablets may also be coated by methods well known in the art

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients Compressed tablets may be prepared by compressing in a suitable machine the active agent in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface-active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active agent

Other formulations suitable for oral administration include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth, pastilles comprising the active agent in an inert base such as gelatin and glycerin, or sucrose and acacia, and mouthwashes comprising the active agent in a suitable liquid carrier

For topical application to the skin, compounds of general formula (Ia), (Ib), (IIa) or (IIb) may be made up into a cream, ointment, jelly, solution or suspension etc Cream or ointment formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia

Compounds of general formula (Ia), (Ib), (IIa) or (IIb) may be used for the treatment of the respiratory tract by nasal, bronchial or buccal administration of, for example, aerosols or sprays which can disperse the pharmacological active ingredient in the form of a powder or in the form of drops of a solution or suspension Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device

Parenteral formulations will generally be sterile

Typically, the dose of the compound will be about 0 01 to 100 mg/kg, so as to maintain the concentration of drug in the plasma at a concentration effective to inhibit PGD_2 at the CRTH2 receptor. The precise amount of a compound of general formula (Ia), (Ib), (IIa) or (IIb) which is therapeutically effective, and the route by which such compound is best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect

Compounds of general formula (Ia), (Ib), (IIa) or (IIb) may be used in combination with other active agents which are useful for the treatment of allergic and other inflammatory diseases mediated by PGD_2 at the CRTH2 receptor

Therefore, the pharmaceutical composition described above may contain one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor

These additional active agents are not necessarily inhibitors of PGD_2 at the CRTH2 receptor – they may have a completely different mode of action Examples of such additional active agents include existing therapies for allergic and other inflammatory diseases including

β2 agonists such as salmeterol,

corticosteroids such as fluticasone;

antihistamines such as loratidine,

leukotriene antagonists such as montelukast;

anti-IgE antibody therapies such as omalizumab;

anti-infectives such as fusidic acid (particularly for the treatment of atopic dermatitis),

anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis),

immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease

CRTH2 antagonists may also be combined with therapies that are in development for inflammatory indications including

other antagonists of PGD_2 acting at other receptors such as DP antagonists,

inhibitors of phoshodiesterase type 4 such as cilonilast;

drugs that modulate cytokine production such as inhibitors of TNFα converting enzyme (TACE),

drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors,

PPAR-γ agonists such as rosiglitazone;

5-lipoxygenase inhibitors such as zileuton

In yet a further aspect of the invention, there is provided a product comprising a compound of general formula (Ia), (Ib), (IIa) or (IIb) and one or more of the agents listed above as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD_2 at the CRTH2 receptor

The invention will now be described in greater detail with reference to the following non limiting examples

Example 1 – Synthesis of [3-(4-Chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 1)

a. Pyridin-2-yl-carbamic acid *tert*-butyl ester

Pyridin-2-ylamine (15.0 g, 0.16 mol) was added slowly in portions over 10 min to a stirred solution of di-*tert*-butyl dicarbonate in *tert*-butanol at room temperature The resulting mixture was stirred at room temperature for 18 h and then concentrated *in vacuo* to leave an off-white solid The solid was triturated with *iso*propanol to give the carbamate (12 9 g, 41 %) as a white solid, Tr = 0 81 min, *m/z* (ES$^+$) $(M+H)^+$ 195 16

b. (3-Iodo-pyridin-2-yl)-carbamic acid *tert*-butyl ester

TMEDA (13 6 ml, 90 0 mmol) was added in one portion to a stirred solution of pyridin-2-yl-carbamic acid *tert*-butyl ester (7 00 g, 36 0 mmol) in anhydrous tetrahydrofuran (150 ml) at -78 °C under nitrogen ^{n}Butyl lithium (86 0 ml, 90 0 mmol, 1.05 M in hexanes) was then added dropwise over 20 min to the solution at -78 °C and the resulting mixture stirred at -78 °C for 30 min. The mixture was allowed to warm to -10 °C and stirred for a further 90 min. The solution was cooled to -78 °C and then iodine (18 3 g, 72 0 mmol) in tetrahydrofuran (25 ml) was added dropwise The resulting mixture was then stirred at -78 °C for 2 h Water (60 ml) and a saturated solution of sodium sulfite (60 ml) were sequentially added to the solution and the resulting mixture was allowed to warm up to room temperature The product was extracted with ethyl acetate (3 x 120 ml) and the combined organic extracts were washed with brine (60 ml), dried and concentrated *in vacuo* to leave a brown residue Purification by flash column chromatography on silica gel eluting with neat heptane to 1 : 1 heptane : ethyl acetate gave the iodo-pyridine (5 00 g, 44 %) as an off-white solid, Tr = 1 09 min, *m/z* (ES$^+$) $(M+H)^+$ 321 18

c. (3-Prop-1-ynyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester

Copper (I) iodide (88 mg, 0 46 mmol) and then dichloro*bis*(triphenylphosphine) palladium (II) (252 mg, 0 36 mmol) were sequentially added to a stirred solution of 3-iodo-pyridin-2-yl)-carbamic acid *tert*-butyl ester (2 30 g, 7 20 mmol) in triethylamine (23 ml) at room temperature in a tube under nitrogen The solution was cooled to -78 °C and then propyne (~ 2 ml, 35 20 mmol), freshly condensed into triethylamine (5 ml) at -78 °C, was then added to the mixture in one portion The vessel was immediately sealed and the resulting mixture was stirred at room temperature for 12 h. The pressure was then released from the vessel and the mixture was diluted with water (100 ml) The product was extracted into ethyl acetate (3 x 100 ml) and the combined organic extracts were then dried and concentrated *in vacuo* to leave a brown residue Purification by flash column chromatography on silica gel eluting with neat heptane to 1 1 heptane ethyl acetate followed by a recrystallisation from ethyl acetate heptane gave the alkyne (3 03 g, 93 %) as a white solid, Tr = 0 99 min, *m/z* (ES^+) $(M+H)^+$ 233 30

d. 2-Methyl-1*H*-pyrrolo[2,3-b]pyridine

Copper (I) iodide (69 mg, 0 36 mmol) was added in one portion to a stirred solution of (3-prop-1-ynyl-pyridin-2-yl)-carbamic acid *tert*-butyl ester (3 00 g, 12 9 mmol) in anhydrous DMF (55 ml) at room temperature The resulting solution was stirred at 80 °C under nitrogen for 16 h The mixture was cooled to room temperature, diluted with ethyl acetate (100 ml) and the resulting solid was filtered to give the azaindole (1 75 g, 100 %) as an off-white solid, Tr = 0 69 min, *m/z* (ES^+) $(M+H)^+$ 133 04

e. 3-(4-Chloro-phenylsulfanyl)-2-methyl-1*H*-pyrrolo[2,3-b]pyridine

4-Chlorobenzenesulfenylchloride (10.0 ml, 3 00 mmol, 0 30 M in toluene) was added dropwise over 5 min to a stirred solution of 2-methyl-1*H*-pyrrolo[2,3-b]pyridine (397 mg, 3 00 mmol) in anhydrous acetonitrile (8 ml) at room temperature The mixture was stirred at room temperature for 4 h and then filtered to leave a white solid The solid was washed with toluene (2 x 5 ml), and then dried *in vacuo* to give the thioether (446 mg, 54 %) as an off-white solid, Tr = 1 34 min, *m/z* (ES^+) $(M+H)^+$ 275 20.

f. [3-(4-Chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid ethyl ester

Sodium hydride (30 mg, 0 73 mmol, 60 % in mineral oil) was added in one portion to a stirred solution of 3-(4-chloro-phenylsulfanyl)-2-methyl-1H-pyrrolo[2,3-b]pyridine (200 mg, 0.73 mmol) in anhydrous DMF (4 ml) at room temperature The solution was stirred at room temperature for 30 min and then ethyl bromoacetate (80 µl, 0 72 mmol) was added dropwise The resulting mixture was stirred at room temperature for 16 h and then concentrated *in* vacuo Purification of the residue by flash column chromatography on silica gel eluting with 2 1 heptane ethyl acetate gave the ethyl ester (40 mg, 15 %) as an off-white solid, Tr = 1 78 min, *m/z* (ES^+) $(M+H)^+$ 361.30.

g. [3-(4-Chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 1)

Lithium hydroxide monohydrate (9 2 mg, 0 22 mmol) and then tetrahydrofuran water (4 ml, 1 1) were sequentially added to [3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid ethyl ester (38 mg, 0.11 mmol) at room temperature The solution was stirred at room temperature for 16 h and then the organic solvent removed *in vacuo.* Water (2 ml) and ethyl acetate (2 ml) were added and the organic solution was then discarded The aqueous solution was adjusted to pH 7 with 1M hydrochloric acid to precipitate a solid which was filtered, washed several times with a small amount of water and then dried to give the carboxylic acid (28 mg, 77 %) as a solid, δ_H (400 MHz, d_6-DMSO) 8 22 (1H, d *J* 4 1 Hz, *Ar*), 7 72 (1H, dd *J* 7 8 1.3 Hz, *Ar*), 7 27 (2H, d *J* 8 6 Hz, *Ar*), 7.11 (1H, dd *J* 7 8, 4 7 Hz, *Ar*), 7 01 (2H, d *J* 8 6 Hz, *Ar*), 4 81 (2H, s, NCH_2CO_2H), 2 45 (3H, s, CCH_3), Tr = 1 53 min, m/z (ES^-) $(M+H)^+$ 332.97

Synthesis of [5-Chloro-3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 2)

The title compound was prepared using the general procedure for the synthesis of [3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 1) using appropriately chosen starting materials δ_H (400 MHz, d_6-

DMSO) 8 29 (1H, d *J* 2 2 Hz, *Ar*), 7 81 (1H, d *J* 2 2 Hz ,*Ar*), 7 37 (2H, d *J* 8 7 Hz, *Ar*), 7 10 (2H, d *J* 8 7 Hz, *Ar*), 4 67 (2H, s, NCH_2CO_2H), 2 52 (3H, s, CCH_3), Tr = 1 71 min, m/z (ES^+) $(M+H)^+$ 367 18

Synthesis of [3-(4-Chloro-phenylsulfanyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 3)

The title compound was prepared using the general procedure for the synthesis of [3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 1) using appropriately chosen starting materials: δ_H (400 MHz, d_6-DMSO) 8 39 (1H, s, *Ar*), 7 77-7 74 (1H, m, *Ar*), 7 47 (2H, d *J* 8.3 Hz, *Ar*), 7 21 (2H, d *J* 8 3 Hz, *Ar*), 4 87 (2H, s, NCH_2CO_2H), 2 63 (3H, s, CCH_3), Tr = 1 61 min, m/z (ES^+) $(M+H)^+$ 351 17

Example 2 – Synthesis of [3-(4-Chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 4)

a. [3-(4-Chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid ethyl ester

Oxone® (409 mg, 0 66 mmol) was added in one portion to a stirred solution of [3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid ethyl ester (80 mg, 0 22 mmol) in 1, 4-dioxane water (10 ml, 4 1) at room temperature The resulting mixture was stirred at room temperature for 24 h A saturated solution of sodium bicarbonate solution (5 ml) was added and the product extracted into ethyl acetate (3 x 10 ml) The combined organic extracts were dried and concentrated *in vacuo* to leave a residue Purification by flash column chromatography on silica gel eluting with 3 1 heptane ethyl acetate to 1 1 heptane . ethyl acetate gave the sulfone (50 mg, 58 %) as a viscous yellow oil, Tr = 1 52 min, m/z (ES^+) $(M+H)^+$ 393 19.

b. [3-(4-Chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 4)

Lithium hydroxide monohydrate (9 mg, 0 20 mmol) and then tetrahydrofuran water (4 ml, 1 1) were sequentially added to [3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid ethyl ester (40 mg, 0 10 mmol) at room temperature. The resulting mixture was stirred at room temperature for 16 h and then the organic solvent was removed *in vacuo* Water (2 ml) and ethyl acetate (2 ml) were added and then the organic layer was discarded The aqueous solution was adjusted to pH 7 with 1M hydrochloric acid to precipitate a solid which was filtered and dried under vacuum to give the carboxylic acid (11 mg, 31 %) as a yellow solid, δ_H (400 MHz, d_6-DMSO) 8 34 (1H, dd *J* 4 7, 1 5 Hz, *Ar*), 8 28 (1H, dd *J* 7 9, 1 6 Hz, *Ar*), 7.99 (2H, d *J* 8 7 Hz, *Ar*), 7 69 (2H, d *J* 8 7 Hz, *Ar*), 7 31 (1H, dd *J* 7 9, 4 8 Hz), 4 61 (2H, s, NCH_2CO_2H), 2 70 (3H, s, CCH_3), Tr = 1 33 min, m/z (ES^+) $(M+H)^+$ 365 02

Synthesis of [5-Chloro-3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 5)

The title compound was prepared using the general procedure for the synthesis of [3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 4) using appropriately chosen starting materials· δ_H (250 MHz, d_6-DMSO) 8 29 (1H, d *J* 2 3 Hz, *Ar*), 8.22 (1H, d *J* 2 3 Hz, *Ar*), 7 96 (2H, d *J* 8 7 Hz, *Ar*), 7 63 (2H, d *J* 8 7 Hz, *Ar*), 4.51 (2H, s, NCH_2CO_2H), 2 61 (3H, s, CCH_3), Tr = 1 47 min, m/z (ES^+) $(M+H)^+$ 399 10

Synthesis of [3-(4-Chloro-benzenesulfonyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 6)

The title compound was prepared using the general procedure for the synthesis of [3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid (Compound 4) using appropriately chosen starting materials δ_H (400 MHz, d_6-DMSO) 8 31 (1H, s, *Ar*), 8 05 (1H, d *J* 9 0 Hz, *Ar*), 8 00 (2H, d *J* 8 3 Hz, *Ar*), 7 65 (2H, d *J* 8 3 Hz, *Ar*), 4 54 (2H, s, NCH_2CO_2H), 2 64 (3H, s, CCH_3), Tr = 1 38 min, m/z (ES^+) $(M+H)^+$ 383 17

Example 3 – Measurement of CRTH2 Antagonist Activity

Materials and Methods

Materials

Calcium-3 dye was purchased from Molecular Devices (Wokingham, UK) Mono-poly resolving medium was obtained from Dainippon Pharmaceuticals (Osaka, Japan) Macs anti-CD16 microbeads were from Miltenyi biotec (Bisley, Surrey) ChemoTx plates were purchased from Neuroprobe (Gaithesburg, MD) Poly-D-lysine coated 96-well plates were obtained from Greiner (Gloucestershire, UK) [^{3}H]PGD_2 was from Amersham Biosciences (Buckinghamshire, UK) [^{3}H]SQ29548 was purchased from Perkin Elmer Life Sciences (Buckinghamshire, UK) All other reagents were obtained from Sigma-Aldrich (Dorset, UK), unless otherwise stated

Methods

Cell culture

Chinese Hamster Ovary cells were transfected with CRTH2 or DP receptors (CHO/CRTH2 and CHO/DP) and were maintained in culture in a humidified atmosphere at 37°C (5% CO_2) in Minimum Essential Medium (MEM) supplemented with 10% foetal bovine serum, 2 mM glutamine, and 1 mg ml^{-1} active G418 The cells were passaged every 2-3 days For radioligand binding assay, cells were prepared in triple-layer flasks or in 175 cm^2 square flasks (for membrane preparation) For calcium mobilisation assay, cells were grown in a 96 well plate 24h prior to the assay at a density of 80,000 cells per well

Preparation of cell membranes

Membranes were prepared either from CHO/CRTH2 and CHO/DP cells, or from platelets (as a source of TP receptors). CHO cells grown to confluency were washed with PBS and detached using a Versene solution (15 ml per flask) When the cells were grown in 175 cm^2 square flask, they were collected by scrapping in PBS The cell suspensions were centrifuged (1,700 rpm, 10 min, 4°C) and resuspended in 15 ml of buffer (1xHBSS, supplemented with 10 mM HEPES, pH 7 3) Cell

suspensions were then homogenised using an Ultra Turrax at setting 4-6 for 20 s The homogenate was centrifuged at 1,700 rpm for 10 min and the supernatant was collected and centrifuged at 20,000 rpm for 1h at 4°C The resulting pellet was resuspended in buffer and stored at -80°C in aliquots of 200-500 µl The protein concentration was determined by the method of Bradford (1976), using bovine serum albumin as standard The platelets were washed by centrifugation at 600xg for 10 min and resuspended in ice-cold assay buffer (10 mM Tris-HCl, pH 7 4, 5 mM Glucose, 120 mM NaCl, 10 µM indomethacin) and directly centrifuged at 20,000 rpm for 30 min at 4°C The resulting pellet was treated as described above

Radioligand binding assays

[^{3}H]PGD_2 (160 Ci/mmol) binding experiments were performed on membranes prepared as described above Assays were performed in a final volume of 100 µl of buffer (1XHBSS/HEPES 10 mM, pH 7 3). Cell membranes (15µg) Cell membranes 15mg were preincubated at room temperature with varying concentration of competing ligand for 15 min [^{3}H]PGD_2 (mol, final concentration) was then added and the incubation continued for a further one hour at room temperature The reaction was terminated by the addition of 200 µl ice-cold assay buffer to each well, followed by rapid filtration through Whatman GF/B glass fibre filters using a Unifilter Cell harvester (PerkinElmer Life Sciences) and six washes of 300 µl of ice-cold buffer. The Unifilter plates were dried at room temperature for at least 1h and the radioactivity retained on the filters was determined on a Beta Trilux counter (PerkinElmer Life Sciences), following addition of 40 µl of Optiphase Hi-Safe 3 (Wallac) liquid scintillation Non specific binding was defined in the presence of 10 µM unlabelled PGD_2 Assays were performed in duplicate

The results of the radioligand binding experiments to the CRTH2 and DP receptors are shown in Tables 1 and 2

Table 1 – Radioligand binding data (Ki on CRTH2 Receptor).

Compounds	Ki (nM)
1	2400
2	747
3	337
4	1020
5	368
6	400

Table 2 – Radioligand binding data (Ki on DP Receptor)

Compounds	Ki (nM)
1	8300
2	>10000
3	>10000
4	>10000
5	>10000
6	>10000

The results of the experiments demonstrate that for compounds of general formula (Ia) and (Ib) the affinity for the CRTH2 receptor is higher than for DP receptor

Compounds of general formula (Ia) and (Ib) bound to CRTH2 receptor expressed in CHO cells with a range of affinity varying from very high to moderate In fact the Ki values determined in competition versus $[^3H]PGD_2$ varied from 500 pM to 1 μM Compounds of general formula (Ia) and (Ib) had no activity (or very weak activity) at the DP receptors The binding selectivity of the illustrated compounds of general formula (Ia) and (Ib) for CRTH2 receptor was greater than 200 fold for CRTH2 receptor, compared to DP receptors However, the inventors have found that by varying the R^8 substitutent of the compounds of general formula (Ia) and (Ib), it is possible to vary the degree of selectivity for the CRTH2 receptor

Calcium mobilisation Assay

Cells were seeded onto poly-D-lysine coated 96-well plates at a density of 80,000 cells per well and incubated at 37°C overnight to allow the cells to adhere Cells were washed twice with HBSS and incubated for 1h at 37°C in 100μl HBSS and

100µl calcium-3-dye (Molecular Devices), supplemented with 4mM probenecid Changes in fluorescence were monitored over a 50s time course with agonist addition at 17s using a Flexstation (Molecular Devices)

Effect of CRTH2 agonists on calcium mobilisation in CHO-CRTH2 cells

PGD_2 caused a dose-dependent increase in intracellular Ca^{2+} mobilisation in CHO/CRTH2 cells, with an EC_{50} = 2 4 ± 0 5nM (n=3) (Figure 2)

Effect of compounds of general formula (Ia) and (Ib) on the calcium mobilisation induced by PGD_2

PGD_2-stimulated Ca^{2+} flux was fully inhibited by the compounds of general formula (Ia) and (Ib) and the IC_{50} value for each compound in the calcium assay was comparable to its Ki value in Radioligand binding IC_{50} values of compounds of general formula (Ia) and (Ib) varied from 5 nM to 1 µM The results for several compounds of general formula (Ia) and (Ib) are shown in Table 3 Increasing doses of the compounds of general formula (Ia) and (Ib) caused a dose-dependent and parallel shift of the PGD_2 dose response curve in CHO/CRTH2 cells, thereby indicating that the compounds are competitive CRTH2 antagonists.

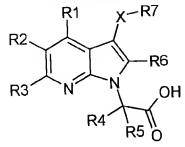
The antagonistic effect of the compounds of general formula (Ia) and (Ib) appears to be CRTH2 selective, since no inhibitory effect was seen with ATP-stimulated Ca^{2+} flux

Table 3 – Inhibition of PGD_2-induced calcium flux

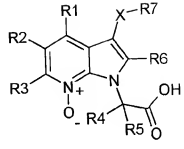
Compounds	IC_{50} (nM)
3	3640
6	572

CLAIMS

1 A compound of general formula (Ia) or (Ib):



Ia



Ib

wherein

R^1, R^2 and R^3 are independently hydrogen, halo, -C_1-C_6 alkyl, -O(C_1-C_6 alkyl), -C_1-C_6 alkyl(C_3-C_7 cycloalkyl), -$CON(R^8)_2$, -SOR^8, -SO_2R^8, -$SO_2N(R^8)_2$, -$N(R^8)_2$, -NR^8COR^8, -CO_2R^8, COR^8, -SR^8, -OH, -NO_2 or -CN,

each R^8 is independently hydrogen or C_1-C_6 alkyl;

R^4 and R^5 are each independently hydrogen, or C_1-C_6 alkyl or together with thecarbon atom to which they are attached form a C_3-C_7 cycloalkyl group,

R^6 is hydrogen or C_1-C_6 alkyl,

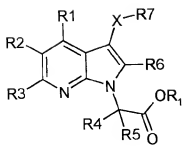
R^7 is C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl or an aromatic moiety, any of which may optionally be substituted with one or more substituents selected from halo, C_1-C_6 alkyl, -O(C_1-C_6)alkyl, -R^{10}, -OR^{10}, $C(R^{10})_2$ -$CON(R^{10})_2$, -SOR^{10} -SO_2R^{10}, -$SO_2N(R^{10})_2$, -$N(R^{10})_2$, -$NR^{10}COR^{10}$, -CO_2R^{10}, -COR^{10}, -SR^{10}, -OH, -NO_2 or -CN,

wherein each R^{10} is independently hydrogen, C_1-C_6 alkyl, aryl or substituted aryl,

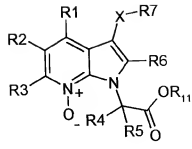
X is -S- or -SO_2-,

or a pharmaceutically acceptable salt, hydrate, solvate, complex or prodrug thereof

2 A compound of general formula (IIa) or (IIb)



IIa



IIb

wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are as defined in claim 1, and

R^{11} is C_1-C_6 alkyl, aryl, $(CH_2)_mOC(=O)C_1$-C_6alkyl, $(CH_2)_mN(R^{12})_2$, $CH((CH_2)_mO(C=O)R^{13})_2$,

m is 1 or 2,

R^{12} is hydrogen or methyl;

R^{13} is C_1-C_{18} alkyl

3. A compound as claimed in claim 1 or claim 2 wherein, independently or in any combination

R^1 is halo or hydrogen,

R^2 is halo or hydrogen,

R^3 is halo or hydrogen,

4 A compound as claimed in claim 3 wherein R^1, R^2 and R^3 are hydrogen.

5 A compound as claimed in any one of claims 1 to 4 wherein R^4 and R^5 are each independently hydrogen or C_1-C_4 alkyl

6. A compound as claimed in claim 4, wherein both R^4 and R^5 are hydrogen

7 A compound as claimed in any one of claims 1 to 6, wherein R^6 is H or C_1-C_6 alkyl

8 A compound as claimed in claim 7 wherein R^6 is hydrogen, methyl or ethyl

9 A compound as claimed in any one of claims 1 to 8 wherein R^7 is an aromatic moiety having one or two rings and substituted with one or more substituents selected from halo, -C_1-C_4 alkyl, -O(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkyl), -R^{10} and -OR^{10}, where R^{10} is aryl or substituted aryl.

10 [[3-(4-Chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
[5-Chloro-3-(4-chloro-phenylsulfanyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid;
[3-(4-Chloro-phenylsulfanyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
[3-(4-Chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid
[5-Chloro-3-(4-chloro-benzenesulfonyl)-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid;
[3-(4-Chloro-benzenesulfonyl)-5-fluoro-2-methyl-pyrrolo[2,3-b]pyridin-1-yl]-acetic acid,
or a C_1-C_4 alkyl ester of one of the above.

11 A process for the preparation of a compound as claimed in claim 1, the process comprising treating a compound of general formula (IIa) or (IIb) as defined in claim 2 with a base

12 A process for the preparation of a compound of general formula (Ib) as claimed in claim 1, the process comprising treating a compound of general formula (Ia) as claimed in claim 1 with an oxidising agent

13 A compound as claimed in any one of claims 1 to 10 for use in medicine, particularly for use in the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

14. The use of a compound as claimed in any one of claims 1 to 10 in the preparation of an agent for the treatment or prevention of diseases and conditions mediated by PGD_2 at the CRTH2 receptor

15. A compound or the use as claimed in claim 13 or claim 14 wherein the disease or condition is allergic asthma, perennial allergic rhinitis, seasonal allergic rhinitis, atopic dermatitits, contact hypersensitivity (including contact dermatitis) conjunctivitis, especially allergic conjunctivitis, food allergies, eosinophilic gastroenteritis, inflammatory bowel disease, ulcerative colitis and Crohn's disease, mastocytosis, another PGD_2-mediated disease, for example autoimmune diseases such as hyper IgE syndrome and systemic lupus erythematus, psoriasis, acne, multiple sclerosis, allograft rejection, reperfusion injury and chronic obstructive pulmonary disease, or rheumatoid arthritis, psoriatic arthritis and osteoarthritis

16 A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 together with a pharmaceutical excipient or carrier

17 A pharmaceutical composition as claimed in claim 16 formulated for oral, rectal, nasal, bronchial (inhaled), topical (including eye drops, buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration

18 A composition as claimed in claim 17 formulated for oral, nasal, bronchial or topical administration

19 A composition as claimed in any one of claims 16 to 18 containing one or more additional active agents useful in the treatment of diseases and conditions mediated by PGD_2 at the CRTH2 receptor.

20 A composition as claimed in claim 19, wherein the additional active agents are selected from

β2 agonists such as salmeterol,

corticosteroids such as fluticasone,

antihistamines such as loratidine,

leukotriene antagonists such as montelukast,

anti-IgE antibody therapies such as omalizumab,

anti-infectives such as fusidic acid (particularly for the treatment of atopic dermatitis),

anti-fungals such as clotrimazole (particularly for the treatment of atopic dermatitis),

immunosuppressants such as tacrolimus and particularly pimecrolimus in the case of inflammatory skin disease

CRTH2 antagonists may also be combined with therapies that are in development for inflammatory indications including.

other antagonists of PGD_2 acting at other receptors such as DP antagonists,

inhibitors of phoshodiesterase type 4 such as cilonilast,

drugs that modulate cytokine production such as inhibitors of TNFα converting enzyme (TACE),

drugs that modulate the activity of Th2 cytokines IL-4 and IL-5 such as blocking monoclonal antibodies and soluble receptors;

PPAR-γ agonists such as rosiglitazone;

5-lipoxygenase inhibitors such as zileuton.

21 A process for the preparation of a pharmaceutical composition as claimed in any one of claims 16 to 20 comprising bringing a compound as claimed in any one of claims 1 to 10 in conjunction or association with a pharmaceutically or veterinarily acceptable carrier or vehicle

22. A product comprising a compound as claimed in any one of claims 1 to 10 and one or more of the agents listed in claim 21 as a combined preparation for simultaneous, separate or sequential use in the treatment of a disease or condition mediated by the action of PGD_2 at the CRTH2 receptor

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Application No:	GB0502316.3	**Examiner:**	Dr Stephen Evans
Claims searched:	1-22	**Date of search:**	25 May 2006

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
X	1, 2, 11-13, 16, 21-22 at least	EP 0773023 A (PFIZER INC) see page 2 line 36 to page 4 line 9
X	1, 2, 11-13, 16, 21-22 at least	WO 2004/074286 A1 (WYETH) see generic formula on page 3 line 30 to page 4 line 16, page 9 lines 2-10 and example 10
X	1, 2, 11-13, 16, 21-22 at least	WO 03/044015 A (THE INSTITUTES FOR PHARMACEUTICAL DISCOVERY LLC) see generic formula on page 3 line 9 to page 6 line 25, examples 189-190

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X}:

C2C

Worldwide search of patent documents classified in the following areas of the IPC

C07D

The following online and other databases have been used in the preparation of this search report

CAS ONLINE, WPI, EPODOC, TXTE